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Dear Wally:

I have learned from Tom Kelly that a decision on guidelines for recombinant DNA experiments involving animal viruses and eukaryotic DNA is imminent and will be taken without prior distribution of a draft as originally planned. At Tom's suggestion I am writing to give my views on the November 5 draft which he showed me.

While I don't want to dwell on the easy generalizations, I do want to say that I recognize there is no single right or wrong set of guidelines regarding animal virus vectors or cloning eukaryotic DNA; in lieu of evidence we all have to rely on judgments of risk. As opposed to the highly speculative estimates of risk, however, the potential benefits in terms of insights into gene action in animal and human cells is (I believe by common consent) very great. The adoption of guidelines which are highly restrictive will seriously impede the development of this field, probably for many years to come, since they are not easily reversed. In my opinion, the guidelines proposed in the November 5 draft <u>are</u> excessively restrictive and will have this effect.

The primary problem regarding animal virus vectors is that all vectors but polyoma require P4 conditions, thus effectively excluding them in a university setting, where much of the creative science is done. While I agree that polyoma is at present a good vector, I hope the committee will define P3-permissive vectors in more general terms which could include other viruses available now or in the near future. Secondly, I believe certain kinds of defective viruses which can infect human cells should be included in the P3-permissive category, since defectiveness adds a substantial biological barrier. Furthermore, many such recombinant viruses already exist in the laboratory (and perhaps in nature) as a result of recombination between primate host cell and viral DNA during propagation, not to mention mutants which are being used universally in animal virus research.

Aside from the above points on animal virus vectors, I would also like to comment on recombinants between primate and prokaryotic

DNA's. I do not see the basis for the sharp escalation of containment requirements (from P3 to P4) when going from nonprimate to primate DNA. I don't know of any good reason to believe that primate DNA is more harmful than nonprimate DNA. Since it is important to be able to clone human (including human mutant) DNA segments for certain kinds of investigations, the requirement for P4 conditions under all circumstances should be examined very carefully.

With these considerations in mind I would like to propose the following guidelines, incorporating the changes indicated above into the November 5 draft.

1. Recombinants between eukaryotic and prokaryotic DNA's.

Experiments involving propagation of recombinant molecules formed between the DNA's of nonprimate eukaryotes and prokaryotic vectors should be carried out under P3 conditions with EK2 vectors. In the case of recombinant molecules containing primate DNA's, the same conditions should apply except that experiments should be done on a scale of one liter or less until a cloned segment of known function and lacking toxigenic genes is obtained. Other experiments with recombinant molecules containing primate DNA's require P4 and EK2 conditions or P3 and EK3 conditions.

2. Eukaryotic host vectors.

a. Recombinant DNA molecules consisting of DNA segments from eukaryotic or prokaryotic cells and a low risk animal virus (CDC classification), and which do not become encapsidated in a virus particle can be used under P2 conditions to infect cultured cells.

b. Defective viruses which do not infect human cells can be used as vehicles under P3 conditions for propagating DNA segments of any nonpathogenic organism. Of the currently known viruses, polyoma has been best studied and is at present the most appropriate vehicle in this category.

c. Defective viruses that can infect human cells and are classified as low risk by CDC can be used under P3 conditions to propagate in cultured cells DNA sequences of any nonpathogenic organism when 1) the viral segment has deletions in transforming and other potentially harmful genes, and 2) the nonviral DNA segment is (a) a highly purified segment of prokaryotic DNA lacking toxigenic genes, or (b) a cloned segment of eukaryotic DNA of known function not coding for toxic products, or (c) a segment of any DNA less than 100 base pairs in length. All other recombinant DNA experiments involving such viruses should be carried out under P4 conditions.

d. Defective low risk viruses can be used as vehicles for propagating in cultured cells segments of the genome of other low risk viruses under P4 conditions.

e. Experiments with recombinant molecules composed of sequences from eukaryotic vectors and agents classified as moderately or highly pathogenic by CDC criteria should not be carried out at this time.

I hope it will be possible to bring these views to the attention of the Committee on Recombinant DNA Molecules.

Sincerely,

Daniel Nathans

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Copy to: Dr. T. J. Kelly
Dr. John Littlefield